Review on the Usage of Oral Medications for Spasticity in a Rehabilitation Hospital in Kuala Lumpur

Wong Shieh Teng[1], Lee Lin Jia[1], Yuzlina binti Muhamad Yunus[1]

[1] Cheras Rehabilitation Hospital, Federal Territory of Kuala Lumpur & Putrajaya, Ministry of Health Malaysia

Abstract

Introduction: Spasticity is a major problem affecting patient's mobility, function and activities of daily living during rehabilitation therapy.

Objective: This study aimed to examine the prescribing pattern of oral medication used for the treatment of spasticity in the Cheras Rehabilitation Hospital.

Methods: All inpatients prescribed with at least one oral drug indicated for spasticity from 1 January 2017 to 30 June 2017 were included in the study. Prescriptions with incomplete data or clinical notes were excluded from the study.

Results: A total of 99 patients who were prescribed with oral spasticity medications were included in this study. Baclofen was the most prescribed oral spasticity drug (81%) followed by Clonazepam (22%) and Eperisone (13%). There were 14 patients who received combination treatment of which 10 patients received Baclofen with Clonazepam combination. Baclofen was the preferred choice of treatment for all the cause of spasticity in HRC. Spinal cord injury recorded the highest usage of Baclofen (35%) and Clonazepam (60%). The diagnosis with the highest mean daily dose (MDD) for Baclofen were cerebral palsy and hypoxic ischemic encephalopathy among adults (60mg/day), and traumatic brain injury among paediatric patients (27.5mg/day). For Clonazepam, spinal cord injury patients had the highest MDD in both adult (1.27mg/day) and paediatrics (0.5mg/day). The MDD of Eperisone was highest among the adult spinal cord injury and cerebral palsy patients (150mg/day). The MDD of oral spasticity medications were lower in patients who received adjunct treatment with *Clostridium Botulinum* Toxin injections for both adult and paediatric patients. Percentage of discontinuation was 14.7% in Baclofen and 33.3% in both Clonazepam and Eperisone.

Conclusion: Patients with spasticity received either single or combination of oral spasticity medications in Cheras Rehabilitation Hospital. Further study is prompted to evaluate the effectiveness and safety of spasticity treatment in this hospital.

Keywords: spasticity, medication, baclofen, clonazepam, eperisone, mean daily dose

NMRR ID: NMRR-17-1391-36617

Corresponding Author: Wong Shieh Teng
Department of Pharmacy, Hospital Rehabilitasi Cheras, Jalan Yaakob Latif, 56000 Kuala Lumpur
Email: wongshiehteng@moh.gov.my

Introduction

Spasticity is defined as disordered sensorimotor control resulting from an upper motor neuron (UMN) lesion, presenting as intermittent or sustained involuntary activation of muscles. It commonly affects people with chronic neurological disorders such as stroke, spinal cord injury, traumatic brain injury, cerebral palsy and multiple sclerosis (1). It greatly affects patient's mobility, function and activities of daily living.

Baclofen is the most widely used oral antispasmodic drug. It is a gamma-aminobutyric acid (GABA) receptor B agonist. It works by reducing calcium influx and suppresses release of excitatory neurotransmitters and thus down-regulates activity of 1a sensory afferents, spinal interneurons and motor neurons (2). It is the most commonly used medication to control spasticity in spinal cord injury (3). The other group of widely used medicines for spasticity is Benzodiazepines, which work via the GABA mediated pathways as well. They increase the affinity of GABA at the GABA receptors and causes presynaptic inhibition and thus a decrease in mono and polysynaptic reflexes. Diazepam and Clonazepam are the oldest and most frequently used Benzodiazepines to treat spasticity (2). On the other hand, the use of Eperisone to treat spasticity has not been

recommended in most of the management guidelines and the number of studies investigating its clinical efficacy is still scarce (3).

Based on the data of Cheras Rehabilitation Hospital (HRC) Pharmacy Census of 2016, Baclofen is among the top twenty most commonly used drugs in the hospital and has been the main choice of treatment for spasticity followed by Clonazepam (4). Eperisone is another newer drug of choice in the treatment of spasticity in HRC. Although all three oral medications have demonstrated efficacy in clinical trials, Clonazepam and Eperisone are not listed for the treatment of spasticity in the Ministry of Health Medicines Formulary, Malaysia (5). This study was carried out to examine the prescribing pattern of oral medications used for the treatment of spasticity in HRC. We wished to understand whether the choice of oral spasticity medications were specific to any specific diagnoses, the common dosages used among patients with spasticity and the trend of drug changes among the patients.

Methods

This is a retrospective cross-sectional study which was conducted using a universal sampling method. All inpatients of HRC diagnosed with spasticity and who were prescribed with at least one oral spasticity medication for the indication of spasticity during their stay in the ward from 1 January 2017 to 30 June 2017 were included from the study. Prescriptions with incomplete data or patients with incomplete clinical notes were excluded.

Demographic data such as age, race and gender were obtained from the Pharmacy Information System (PhIS). Information on patient's disease and medication therapy was obtained from the Pharmacist Clinical Notes (forms CP1 and CP2). Disease data collected were the cause of spasticity or diagnosis, factors that could affect the dose of spasticity treatment such as the presence of side effects, and the date of event or illness to estimate the length of disease or illness. Patient's medication therapy was recorded at two points, which were the first and last prescriptions within the period of 1 January 2017 to 30 June 2017. Medication information collected were dosage and frequency of oral medication for spasticity treatment, other drugs that may affect the dosage of oral antispasmodic prescribed, the date the drug was started and stopped, and the reason for stopping if available. Data was collected with a Data Collection Form.

The data were collected and analysed descriptively using the Microsoft Excel Spreadsheet Software version 2010. Discrete data were presented as frequency (n) and percentage while continuous data were expressed as mean (standard deviation (SD)).

Results

A total of 106 patients with at least one of the study medications indicated for the treatment of spasticity were identified but 7 patients were excluded due to incomplete data. The final number of patients included in the study was 99 patients. The majority of patients were male (n= 67, 68%) with the mean age of 35 (SD 20) years old and were of the Malay ethnic (n=68, 69%) (Table 1). Traumatic brain injury and spinal cord injury were the most common causes of spasticity among the study population, both with 31 (31%) patients. Majority of the patients were newly diagnosed or had recent events of spasticity with the length of illness between zero to twelve months (n=33, 44%).

Table 2 compared the utilisation of each drug in the first and the final prescriptions within the six-month study period. There were 74 (75%) patients that received at least one oral spasticity medication during the initial stage of study while the final stage of study recorded a total of 92 (93%) patients prescribed with oral spasticity medications. Findings showed that 25 (25%) of the patients were newly prescribed with oral spasticity medication. Majority of patients received spasticity monotherapy (n=78, 85%) and Baclofen was the most prescribed oral spasticity medication (n= 75, 82%).

Table 3 showed the use of oral spasticity medication by diagnoses. Baclofen was the preferred choice of treatment for all causes of spasticity in HRC. Table 4 tabulated the mean daily dose (MDD) of Baclofen, Clonazepam and Eperisone by the causes of spasticity. The MDD of Baclofen was the highest for cerebral palsy and hypoxic ischemic encephalopathy in adults (60mg/day). Among the paediatric patients, traumatic brain injury group had the highest MDD of Baclofen (25.5mg/day). Eperisone was not used in paediatric patients in HRC. The MDD of Eperisone was the highest among the adult spinal cord injury and cerebral palsy groups with 150mg/day.

The percentage of discontinuation was 14.7% in Baclofen and 33.3% in both Clonazepam and Eperisone when compared to the initial stage of the study. As shown in Figure 1, Baclofen had the highest number of drug discontinuation, dose increment and dose reduction among the three oral spasticity medications. It was stopped in one case due to allergic reaction and in one paediatric patient due to change of treatment to intrathecal Baclofen. Clonazepam was stopped in one case due to dizziness. The reason for Eperisone discontinuation was not documented. There were five cases of switching antispasmodic therapy whereby three patients switched from Baclofen to Eperisone, one with combination Baclofen and Clonazepam switched to Eperisone and one with Baclofen switched to Clonazepam.

Table 5 showed the effect of adjunct medications on the MDD of oral spasticity medications. The MDD of both Baclofen and Clonazepam was lower in adult patients receiving oral adjunct treatment with Gabapentin (32.2mg/day and 0.8mg/day respectively). The MDD of all three oral spasticity medications were lower in both adult and paediatric patients who received adjunct treatment with *Clostridium Botulinum* Toxin injections.

Table 1: Demographic and baseline characteristics of patients included in the study (N=99)

Characteristics	n (%) / mean (SD)
Age, year, mean (SD)	35 (20)
Age, n (%)	
< 18	21 (21)
18 – 64	69 (70)
≥ 65	9 (9)
Gender, n (%)	
Male	67 (68)
Female	32 (32)
Ethnicity, n (%)	
Malay	68 (69)
Chinese	21 (21)
Indian	10 (10)
Diagnosis, n (%)	
Traumatic brain injury	31 (31)
Spinal cord injury	31 (31)
Stroke	19 (19)
Cerebral palsy	12 (12)
Hypoxic ischemic encephalopathy	3 (3)
Others	3 (3)
Length of illness (months)*, n (%)	
0 – 12	33 (44)
13 – 60	27 (36)
61 – 120	9 (12)
> 120	6 (8)

* The sample size for length of illness was only 75 patients (N=75) due to incomplete data.
Abbreviation: SD – standard deviation

Table 2: Utilisation of oral spasticity medications at the initial and final stage of the study

Utilisation	Initial Stage, n (%)	Final Stage, n (%)
Therapy		
Monotherapy	60 (81)	78 (85)
Combination therapy	14 (19)	14 (15)
Medication		
Baclofen	68 (92*)	75 (82*)
Clonazepam	15 (20*)	20 (22*)
Eperisone	6 (8*)	12 (13*)

* The percentage did not total up to 100% as some patients received two or more medications

Table 3: Patients on oral spasticity medication in accordance to diagnoses or illness

Cause of Spasticity	Baclofen, n (%)	Clonazepam, n (%)	Eperisone, n (%)
Traumatic brain injury	24 (32)	0	6 (50)
Spinal cord injury	26 (35)	12 (60)	3 (25)
Stroke	8 (11)	6 (30)	2 (17)
Cerebral palsy	12 (16)	1 (5)	1 (8)
Hypoxic ischemic encephalopathy	2 (3)	0	0
Others*	3 (4)	1 (5)	0
Total	75	20	12

* congenital rubella syndrome, congenital toxoplasmosis, neurodegenerative brain disorder

Table 4: Mean daily dose of Baclofen, Clonazepam and Eperisone according to the causes of spasticity

Cause of Spasticity	Mean Daily Dose (SD), mg/day					
	Baclofen		Clonazepam		Eperisone	
	Adult	Paediatric	Adult	Paediatric	Adult	Paediatric
TBI	28 (13.5)	25.5 (11.1)	-	-	117 (25.8)	-
SCI	37 (18.0)	-	1.3 (0.98)	0.5	150	-
Stroke	38 (19.2)	-	0.7 (0.6)	-	100	-
CP	60	22 (12.4)	2	-	150	-
HIE	60	15	-	-	-	-
Others*	60	19 (12.8)	0.5	-	-	-

*congenital rubella syndrome, congenital toxoplasmosis, neurodegenerative brain disorder

Abbreviation: SD – standard deviation; TBI - traumatic brain injury; SCI - spinal cord injury; CP - cerebral palsy; HIE - hypoxic ischemic encephalopathy

Figure 1: Treatment modification within the six-month study period

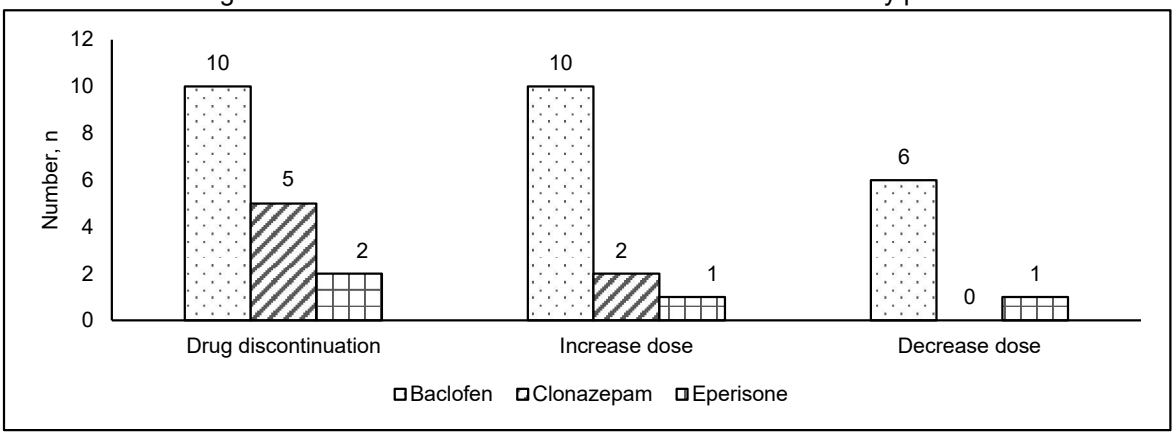

Table 5: MDD of Baclofen, Clonazepam and Eperisone when used concurrently with medicines that may affect spasticity treatment

Concurrent medications	Mean Daily Dose (SD), mg/day			
	Baclofen		Clonazepam	Eperisone
	Adult	Paediatric	Adult	Adult
Gabapentin	32.2 (11.6)	-	0.8 (0.3)	133.3 (28.9)
Pregabalin	43.0 (11.0)	-	1.3 (0.4)	150.0
Clostridium Botulinum toxin type A	24.4 (15.4)	15.0 (5.3)	0.5 (0.5)	100.0
None	34.4 (18.2)	22.8 (12.7)	1.2 (0.7)	116.7 (25.8)

Discussion

From the HRC Pharmacy Census of 2016 (4), Baclofen was among the top 20 most commonly used drugs in HRC. It is one of the oldest drugs used to treat spasticity. Although Baclofen still remains the main drug of choice for the treatment of spasticity, there was indeed a slight shift in the choice of antispasmodic agent in HRC over the six-month study period. The percentage of Baclofen usage had decreased a little and there had been a small increase in the usage of Clonazepam and Eperisone for the treatment of spasticity.

There has not been much research investigating the effectiveness of combination therapy using multiple medications (6). However, spasticity treatment combining Baclofen and Clonazepam, being the most common combination, has been utilised in HRC with 90% for spinal cord injury patients. A study conducted by Chendrowski on the efficacy of Clonazepam and Baclofen found that both drugs were significantly more effective than placebo. There was no significant difference in terms of efficacy between Baclofen and Clonazepam. (7) Although combination therapy was not investigated, the study concluded that there was a possibility that the combination of Baclofen and Clonazepam may be more effective than either drug alone (7). Nonetheless, there seemed to be a decrease in the use of combination therapies over the six-month period in HRC. There were five cases of switching from combination to monotherapy and only one case of switching from mono to combination therapy.

Open-label studies have shown that oral Baclofen improved spasticity in 70% to 87% of patients whereas 75% to 96% of patients had improvement in spasms. Some of the major side effects of Baclofen are sedation, weakness, vertigo and psychological disturbances (8,9). In a double-blinded cross-over study to investigate the effects of low dose Benzodiazepine to manage spasticity among children with cerebral palsy, Clonazepam significantly reduced spastic restraint compared to placebo (10).

Overall, there was lack in high-quality evidence supporting the use of oral spasticity medications to treat specific diagnosis and to help guide the choice of one medication over the other (11). According to a review by Rabchevsky *et al.*, Baclofen is currently the pharmacologic agent of choice for the treatment of spinal cord injury-induced spasticity (12). This was reflected in this study as the use of Baclofen was used most in the spinal cord injury group. The MDD of Baclofen used in HRC ranged from 28mg/day to 60mg/day. This was supported by a risk-benefit assessment by Dario *et al*. which showed that the effective and well tolerated dose of Baclofen ranged from 30mg/day to 80mg/day (8).

In a review by Chang *et al*., it was demonstrated that Benzodiazepines had the tendency to act primarily on flexor reflexes. Benzodiazepines were better suited to treat spasticity of spinal origin than cerebral origin spasticity because spinal origin spasticity had an inclination to affect flexor reflexes (6). This explained the findings that Clonazepam was most highly used in spinal cord injury patients in this study and was least prescribed for patients with spasticity of cerebral origin.

Eperisone was mostly used for treatment of spasticity among traumatic brain injury patients in HRC with relatively low MDD of 117mg/day. In a cross-over, placebo-controlled trial conducted by Bresolin *et al*., they discovered a significant reduction in muscle tone compared to baseline measures among patients with spastic palsy. The ability to walk was also seen to have improved significantly with patients on 300mg/day of Eperisone. The incidence of adverse effects in this study was few and was deemed to be mild or moderate and thus suggested a positive tolerability profile (13). When compared to Baclofen, both drugs significantly improved functionality of lower limbs but only Eperisone improved this parameter in the upper limbs. Although both drugs decreased muscle hypertonia, only Eperisone improved joint range of motion in week two of the study. These recent findings could mean that Eperisone is a potential alternative treatment for spasticity. Nonetheless, further clinical investigations need to be carried out to ensure its safety and efficacy (14).

An analysis was carried out to determine the effect of certain concurrent medication such as Gabapentin, Pregabalin and Botulinum Toxin injection on the MDD of oral Baclofen, Clonazepam and Eperisone. The MDD of both Baclofen and Clonazepam was lower in patients with adjunct Gabapentin treatment. Similarly, a study by Chang *et al*. showed that the use of Gabapentin alone demonstrated a reduction in the Ashworth scale compared to placebo. However, it is rarely used as monotherapy (6). On the contrary, Pregabalin which is considered to be the next generation of Gabapentin did not show reduction in MDD for all treatment groups in this study. However, there was a retrospective case study which concluded that Pregabalin may be effective in reducing spasticity in a portion of patients with spinal cord injury (12). The findings in this study could not conclude whether the adjunct treatments would affect the MDD of spasticity medications, but it

could be seen that the MDD of oral treatments were generally lower in patients who received Botulinum toxin injections. The reason for this could be that these patients only experienced focal spasticity and thus a higher dose of systemic agents were not needed.

There were several limitations to this study, such as, dependency on the accuracy of written records, incomplete clinical data (especially the reason for discontinuation of treatment), and difficult to control bias and confounders. The recommendation would be to conduct a prospective observational study for the next stage of this research.

Conclusion

HRC utilises a variety of combination and monotherapy in the treatment of spasticity. The exact choice of treatment for spasticity of varying origin remains unclear. Further study is needed to evaluate the safety and efficacy of spasticity treatment.

Acknowledgement

We would like to thank the Director General of Health Malaysia for his permission to publish this article. We would like to thank the Deputy Director of Health (Pharmacy) in Kuala Lumpur & Putrajaya, the Director of HRC, Clinical Research Centre of HRC and those who have helped provide us with the information and data needed to complete this study.

Conflict of Interest Statement

The author declared no conflict of interest

References

1. Sheean G. The pathophysiology of spasticity. *European Journal of Neurology.* 2002; 9(1):3-9.
2. Kheder A, Padmakumari K. Spasticity: Pathophysiology, Evaluation and Management. *Practical Neurology.* 2012; 12:289–298
3. Krach LE, Pharmacotherapy of Spasticity: Oral Medications and Intrathecal Baclofen. *J Child Neuro*. 2001 16(1):31-36
4. Cheras Rehabilitation Hospital. 2016. *Cheras Rehabilitation Hospital Pharmacy Census of 2016*. (*unpublished*)
5. Pharmaceutical Services Programme, Ministry of Health Malaysia. 2017. *Ministry of Health Malaysia Drug Formulary*. Available at: https://www.pharmacy.gov.my/v2/en/apps/fukkm
6. Chang, E, Ghosh, N, Yanni, D, et al. A review of spasticity treatments: Pharmacological and interventional approaches. *Crit Rev Phys Rehabil Med.* 2013; 25(1-2): 11-22.
7. Cendrowski W, Sobczyk W. Clonazepam, Baclofen and Placebo in the Treatment of Spasticity. Eur Neurol. 1977; 16: 257-262
8. Dario A, Tomei G. A Benefit-Risk Assessment of Baclofen in Severe Spinal Spasticity. Drug Safety 2004; 27(11): 799-818
9. Scheinberg A, Hall K, Lam LT, O'Flaherty S. Oral baclofen in children with cerebral palsy: A double-blind cross-over pilot study. Journal of Paediatrics and Child Health. 2006; 42: 715-720
10. Dahlin M, Knutsson E, Nergardh A. Treatment of Spasticity in Children with Low Dose Benzodiazepine. Journal of the Neurological Sciences. 1993; 117: 54-60
11. Watanabe, T. Role of oral medication in spasticity management. *American Academy of Physical Medication and Rehabilitation*. 2009; 1: 839-841.
12. Rabchevsky, A, Kitzman, P. Latest approaches for the treatment of spasticity and autonomic dysreflexia in chronic spinal cord injury. Neurotherapeutics. 2011; 8(2): 274-282.
13. Bresolin N, Zucca C, Precori A. Efficacy and tolerability of eperisone in patients with spastic palsy: a cross-over, placebo-controlled dose-ranging trial. Eur Rev Med Pharmacol Sci. 2009; 13(5): 365-370.
14. Bresolin N, Zucca C, Precori A. Efficacy and Tolerability of Eperisone and Baclofen in Spastic Palsy: a Double-Blind Randomized Trial. Adv Ther. 2009; 26(5): 563-573.